RECEIVED
CENTRAL FAX CENTER
FEB 10 2006

Attorney Ref. No.: 082137-0280655

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION OF

Robert B. DICKSON *et al.*

Application No. 09/936,333

Filed: March 5, 2002

Title: MATRIPTASE, A SERINE PROTEASE AND ITS APPLICATIONS

Examiner: Zachariah Lucas

Group Art Unit: 1648

Conf. No.: 4097

February 10, 2005

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This request is submitted in response to the final office action dated August 10, 2005, and the Advisory Action dated November 30, 2005, and is timely filed, as it is accompanied by a request for an extension of time to file in the third month.

Further to the Notice of Appeal filed herewith, and prior to the filing of an Appeal Brief, the applicants respectfully request review of the rejection of claims 16, 18, and 34-36 under 35 U.S.C. §112, first paragraph, for an alleged lack of written description of the claimed invention.

The applicants have discovered that matriptase, a cancer-associated protease, is produced in two forms: an inactive single-chain form (zymogen) and an active, two-chain form, and that antibodies can be produced against matriptase that distinguish between the single-chain and two-chain forms by binding with greater affinity to the two-chain form than to the single-chain form. The applicants have further demonstrated that Hepatocyte Growth Factor Activator Inhibitor-1 (HAI-1) binds to the active two-chain form of matriptase and inhibits the active protease. Prior to the applicants' discovery, it was not known that matriptase was produced in both the inactive single-chain form and the active two-chain form, or that antibodies could be obtained that bind with greater affinity to the two-chain form than to the single-chain form of the enzyme.

PAGE 5/9 * RCVD AT 2/10/2006 4:57:44 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-6/30 * DNIS:2738300 * CSID:703 770 7901 * DURATION (mm-ss):02-50

Claim 16 of the present application is directed to "[a]n isolated antibody or immunologically reactive fragment thereof which selectively binds with greater affinity to a two-chain (active) form of matriptase of a human than to a single-chain (zymogen) form of matriptase of said human." Claims 18 and 34-36 depend from claim 16. Claim 36 is directed to "[t]he antibody or immunologically reactive fragment thereof of claim 16, which binds to the two-chain (active) form of a matriptase protein that is present in a complex comprising HAI-1 or a fragment thereof."

The specification sets forth reliable screening and assay procedures by which the claimed antibodies can be obtained. In particular, Example 5 describes screening 80 hybridoma clones that bind specifically to the 95 kDa matriptase/HAI-1 complex under non-boiled conditions and to uncomplexed matriptase after boiling, and the identification of hybridomas that produce two antibodies, referred to as M69 and M123, that produce antibodies that selectively bind with greater affinity to the two-chain (active) form of a human matriptase than to the single-chain (zymogen) form of human matriptase (*e.g.*, see page 90, line 7, to page 91, line 10). The electrophoretic assay used in the disclosed example to identify antibodies according to claim 16 is a generic assay that detects binding to any portion of either the single-chain form or the two-chain form of matriptase.

On page 6 of the final office action, the examiner rejected claims 16, 18, and 34-36 under 35 U.S.C. §112, first paragraph, for alleged lack of written description of the claimed invention. The examiner alleges that the rejected claims contain subject matter that is "not described by the specification in such a way as to convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." The examiner acknowledges the applicants' disclosure of two examples of the claimed antibodies (antibodies M69 and M123) that selectively bind with greater affinity to the two-chain, active form of human matriptase than to the single-chain, zymogen form of the protein. However, the examiner does not consider the description of the claimed invention to be sufficient under 35 U.S.C. §112, first paragraph, because the specification does not describe or provide a means to identify the epitopes on matriptase that are targeted by the claimed antibodies, "so as to allow those in the art to identify and particular structure that may be targeted which structure would correspond to an epitope present in the two-chain but not in the zymogen form of matriptase" (*see* pages 7-8 of the official action).

The examiner further rejected claim 36, which specifies an antibody that binds with greater affinity to the two-chain form of a matriptase protein that is present in a complex comprising HAI-1. The examiner acknowledges that antibody M123 is an example of an antibody according to claim 36, but alleges that the disclosure of a single example of such an antibody is insufficient descriptive support for claim 36, for reasons similar to those given for the rejection of claim 16.

The examiner has maintained the rejection of claims 16, 18, and 34-36 under 35 U.S.C. §112, first paragraph, for lack of written description, in the advisory action. In

paragraph no. 11 of the advisory action, the examiner gives the following three reasons for maintaining the rejection of the claims:

a) The examiner does not consider the disclosed antibodies M69 and M123 that bind with greater affinity to the two-chain than the one-chain form of matriptase to be representative of the claimed genus, because the specification does not provide information about epitopes on matriptase which can be bound by antibodies encompassed by the claims, other than the epitopes bound by the two disclosed antibodies. In support, the examiner states that the disclosure of multiple species within a claimed genus does not necessarily demonstrate possession of the genus "where there is unpredictability in performance of certain subspecies...other than those enumerated," citing In re Smyth, 178 U.S.P.Q. 279 at 284-5 (CCPA 1973), and University of California v. Eli Lilly and Co., 43 U.S.P.Q.2d 1398 at 1405 (Fed. Cir. 1997).

b) Referring to the disclosed method for screening to identify antibodies that bind with greater affinity to the two-chain than the single-chain form of matriptase, the examiner states that "methods of screening are not sufficient to demonstrate possession (therefore descriptive support) for a claimed genus," and that "it is the identification of the specific biomolecules which is required," citing University of Rochester v. G.D. Searle & Co., 69 U.S.P.Q.2d 1886 at 2163 (Fed. Cir. 2004), and M.P.E.P. §2163 II.A.2(a).

c) The examiner recognizes that the description of an isolated protein may be sufficient to support a generic claim directed to any antibody that binds to the protein. However, the examiner considers that the fact that the antibodies of the rejected claims selectively bind with greater affinity to the two-chain than the single chain form of matriptase necessitates a much more stringent requirement for description of the claimed antibodies; *i.e.*, the examiner alleges that the specification must describe the specific epitopes on matriptase to which the antibodies bind in order to satisfy the requirement for written description under 35 U.S.C. §112, first paragraph.

It is respectfully submitted that the application describes the antibodies to which claims 16, 18, and 34-36 are directed in sufficient detail that one skilled in the art can reasonably conclude that the applicants had possession of the claimed invention; therefore, the application satisfies the requirement for written description under 35 U.S.C. §112, first paragraph, for the rejected claims.

The amount and type of information required to satisfy the requirement for written description for a claimed invention under 35 U.S.C. §112, first paragraph, is dependent on the nature of the invention, and each case must be decided on its own facts. *See* In re Smyth, 178 U.S.P.Q. 279 at 284 (CCPA 1973). The requirement for written description under 35 U.S.C. §112, first paragraph, for claims directed to antibodies that bind to an antigenic protein can be satisfied solely by description of the antigenic protein with reference to such parameters as the molecular weight or amino acid sequence of the antigenic protein. For example, U.S. Patent No. 6,995,005, issued February 7, 2006, describes the isolation of a microbial ester-group-cleaving enzyme and has claims directed to monoclonal and polyclonal antibodies that

bind specifically to the disclosed enzyme (*see* claims 7 and 8), even though the application does not describe having obtained any antibodies directed against the disclosed protein.

The applicants submit that the acceptance by the USPTO of the description of an antigenic protein as being sufficient to satisfy the written description requirement of 35 U.S.C. §112, first paragraph, for antibodies directed to the described protein is, to a large degree, based on the recognition by persons of skill in the art that the mammalian antibody repertoire is extremely large, and that known immunological methods enable one to reproducibly produce multiple antibodies that bind specifically to an antigen of interest. This is equally true for the antibodies to which claims 16, 18, and 34-36 of the present application are directed. The applicants have described and characterized two structurally distinct forms of matriptase, a single-chain (zymogen) form and a two-chain (active) form, and have demonstrated that antibodies can be obtained that bind with differential affinity to the two forms; presumably because they recognize and bind to structural features on the two-chain form that are altered or absent on the single-chain form. The preparation of antibodies that recognize structural features on the two-chain (active) form of matriptase that are altered or absent on the single-chain (zymogen) form of the protein is directly analogous to preparing antibodies against an antigenic protein. Accordingly, the proper standard for determining compliance with the written description requirement of 35 U.S.C. §112, first paragraph, for the claimed antibodies should be similar to that which is used in determining compliance with the written description requirement for claims directed to antibodies that target an antigenic protein. In fact, by obtaining and characterizing two different antibodies that bind with greater affinity to the two-chain (active) form than to the single-chain (zymogen) form of matriptase, the applicants have provided significantly more descriptive support for the claimed antibodies than is generally required by the USPTO, as noted above.

The examiner's allegation that the written description is inadequate because it does not identify epitopes other than those bound by disclosed antibodies M69 and M123 has no legal or scientific basis. The examiner relies on In re Smyth, 178 U.S.P.Q. 279 at 284-5 (CCPA 1973), and University of California v. Eli Lilly and Co., 43 U.S.P.Q.2d 1398 at 1405 (Fed. Cir. 1997), for the proposition that the disclosure of multiple species within a claimed genus may not demonstrate possession of the genus "where there is unpredictability in performance of certain subspecies...other than those enumerated." However, as noted above, "each case must be decided on its own facts." *See* In re Smyth, (p. 284). The issue in question in In re Smyth, was whether a claim directed to a fluid separator element was adequately described by disclosure of gaseous separator elements; and the issue in question in University of California v. Eli Lilly and Co. was whether description of a rat cDNA encoding insulin provides adequate descriptive support for claims generically directed to a mammalian cDNA encoding insulin, or for a claim directed to cell containing a human cDNA encoding insulin. The claims of the present application are directed to antibodies, and the level of predictability and amount and type of description required to satisfy the written description requirement under 35 U.S.C. §112, first paragraph, are unique to the antibody art.

With regard to the examiner's allegation that the application must identify the epitopes bound by the claimed antibodies, the applicants submit that one of skill in the art would reasonably expect that there are numerous structural features present on the two-chain form, in addition to the epitopes bound by antibodies M69 and M123, to which antibodies according to the rejected claims can bind. The limited screen of 80 hybridomas described in the present application (*see* page 90) identified two antibodies that bind to the two-chain form with greater affinity than to the single-chain form of matriptase (a 1:40 success ratio), and one of skill in the art would reasonably expect that additional examples of the claimed antibodies, including antibodies that bind to epitopes other than those bound by the disclosed antibodies, would be obtained by screening more hybridomas as described in the application. Description of the specific epitopes on the two-chain form of matriptase to which the claimed antibodies bind is not required to demonstrate the applicants' possession of the claimed invention to one of skill in the art, just as it is not required that an applicant describe epitopes on the surface of an antigenic protein that are bound by antibodies in order to satisfy the requirement for written description for claims directed to antibodies that target said protein.

For the foregoing reasons, the applicants respectfully submit that one of skill in the art can reasonably conclude that the applicants had possession of the claimed invention, and that the application satisfies the requirement for written description under 35 U.S.C. §112, first paragraph, for rejected claims16, 18, and 34-36. Accordingly, withdrawal of the rejection of claims 16, 18, and 34-36 under 35 U.S.C. §112, first paragraph, for failure to comply with the written description requirement, is respectfully requested.

Please charge any fees or credit any overpayments associated with the submission of this response to Deposit Account Number 03-3975.

Respectfully submitted,

Date: February 10, 2006

By _____

Thomas A. Cawley, Jr., Ph.D.
Reg. No. 40944
Tel. No. 703.770.7944
Fax No. 703.770.7901

PILLSBURY WINTHROP SHAW PITTMAN LLP
P.O. Box 10500
McLean, VA 22102
703.770.7900